REMARKS/ARGUMENTS

Reconsideration and withdrawal of the rejections of this application and consideration and entry of this paper are respectfully requested in view of the herein remarks and accompanying information, which place the application in condition for allowance.

I.) Status of Claims and Formal Matters

Claims 1-12 were pending in this application. Claims 1-3 and 5-6 and 8-12 have been amended, without prejudice, without admission, without surrender of subject matter, and without any intention of creating any estoppel as to equivalents. No new matter has been added.

The Claims have been rejected under 35 U.S.C. 103(a) as being obviousness over three separate combinations of references. Each of the claim rejections will be addressed in detail below. Based on these arguments, reconsideration of the Section 103 rejections is earnestly requested.

II.) The Claim Rejections under 35 U.S.C. § 103(a) are Overcome:

A.) Rejection over Nickel et al., US 6,093,704 and Nickel et al., US 6,696,428 and Nössner et al., US 6,172,050 in view of Calabresi et al., Goodman & Gilman's, The Pharmacological Basis of Therapeutics, Ninth Edition.

Claims 1-12 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Nickel et al., US 6,093,704 and Nickel et al., US 6,696,428 and Nössner et al., US 6,172,050 in view of Calabresi et al., Goodman & Gilman's, The Pharmacological Basis of Therapeutics, Ninth Edition. The Office Action contends that the three primary references (Nickel, Nickel and Nössner) teach that alkylphosphocholines, as those presently claimed as part of a combination therapy, could be used in the treatment of breast cancer. Moreover, although the primary references do not teach the claimed combination, the Office Action argues that Calabresi teaches

that drugs are generally more effective in combination and may be synergistic through biochemical Interactions.

Applicants argue that the Examiner is making far too big of a leap when stating that the primary references can be combined with Calabresi in such away as to render the present claims obvious. Calabresi presents an overview of chemotherapeutic reagents developed as of 1995. In Table X-1 of Calabresi, over forty specific compounds are mentioned and other compounds are discussed as being in clinical development. On page 1230, Calabresi gives some guidance regarding combination therapy in the treatment of cancer. No specific combinations are mentioned and no specific types of cancer are referred to. In short, Calabresi is advocating that it may be possible to develop effective combinations therapies in the treatment of cancer if the correct drugs are chosen and the right conditions are met.

Based on the Examiner's interpretation of Calabresi, it would seem as though it would be obvious to choose any given combination of chemotherapeutic reagents to develop a more effective treatment against any given type cancer. However, such an approach neglects pharmacokinetic profiles, toxicity, drug-drug interactions and mechanism of action. Also, such an approach ignores the fact that a single combination effective against one type of cancer may be completely ineffective towards the treatment of other types of cancer. What one is left with is a plethora of different drug combinations to be tested against a multitude of different types of cancer. Thus, choosing the correct combination of therapeutics for a given type of cancer cannot be considered obvious. Moreover, because of the large array of possible combinations of drugs, finding a combination that is effective and synergistic towards the treatment of mammary carcinoma would not be expected to be successful at the time the invention was made.

Outside of the blanket statements in Calabresi regarding combinations, there is nothing in either Calabresi or the primary references that would motivate one of ordinary skill in the art to use a combination of a heterocyclic alkylphosphocholine with one of the claimed chemotherapeutic reagents for the treatment of breast cancer. The two Nickel references are directed towards using an alkylphosphocholine in combination with a dopamine receptor agonist. Applicants do not see how such a combination is relevant to the presently claimed invention. The goal of the Nickel references is to develop a combination that would alleviate side effects

normally associated with the administration of alkylphosphocholines. The Examiner asks what the references would suggest to one of ordinary skill in the art? Certainly, if the goal was to reduce side effects, one would not consider adding another reagent such as a cisplatinum or a cyclophosphamide, which are known to cause serious side effects.

The other primary reference, Nössner, is discussed in greater detail in Section IIC below. Nössner does talk about using cytostatics in the treatment of mammary carcinomas (see Column 19 of Nössner). Nössner concludes that while heterocyclic alkylphosphocholines are effective in such treatment, "standard cytostatics (e.g., cyclophosphamide, cisplatin and Adriamycin) proved relatively ineffective." To one of ordinary skill in the art, such a statement would suggest that one of these cytostatics should not be used in the treatment of mammary carcinomas. Thus, the Applicants finding regarding the synergistic effect of heterocyclic alkylphosphocholines in combination with these cytostatics is unexpected and surprising.

In short, Applicants believe that the Examiner is using impermissible hindsight based on the Applicant's disclosure in establishing this section 103 rejection. Applicants remind the Examiner that it is impermissible to engage in a hindsight reconstruction of the claimed invention, using the Applicant's structure as a template, and selecting elements from references to fill in the gaps. *Interconnect Planning*, 744 F.2d 1132, 1143 (Fed. Cir. 1985).

Consequently, withdrawal of the Section 103 rejection is earnestly requested.

B.) Rejections over Hilgard et al. Cancer Chemother. Phamacol., (1993) 32:90-95 in view of Stekar et al. European J. of Cancer, (1995) Vol. 31(3) pp 372-374.

Claims 1-2, 5-6 and 9-12 were rejected under 35 U.S.C. 103(a) as being unpatentable over Hilgard et al. Cancer Chemother. Phamacol, (1993) 32:90-95 in view of Stekar et al. European J. of Cancer, (1995) Vol. 31(3) pp 372-374. The Office Action contends that Hilgard teaches miltefosine in combination with cisplatin for the treatment of mammary carcinoma. The Office Action further alleges that Stekar teaches that the drug miltefosine is administered prior to the administration of cyclophosphamide.

To establish *prima facie* obviousness of the claimed invention, all of the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974).

The claims 1-3, 5-6 and 8-12 have now been amended such that compound of Formula I (e.g. miltefosine) are no longer claimed as part of the combination therapy. These claims, as amended, only include combinations comprising cyclic alkylphosphocholines of Formula II in combination with an antitumor medication. Neither Hilgard or Stekar teach or suggest a method of treating mammary carcinoma with a combination of compounds of Formula II and an approved antitumor substance. Because the references in combination do not teach all of the limitations currently claimed, a *prima facie* case of obviousness has not been established.

Independent claim 2 has also been amended such that the platinum-based and cyclophosphamide compounds are no longer included as part of the Markush group of antitumor substances. Thus, the cited references fails to teach the presently claimed combination therapy. Accordingly, a *prima facie* case of obviousness has not been established.

Consequently, withdrawal of the Section 103 rejection is earnestly requested.

C.) Rejections over Hilgard et al. Cancer Chemother. Phamacol, (1993) 32:90-95 and Stekar et al. European J. of Cancer, (1995) Vol. 31(3) pp 372-374 in view of Nössner et al. U.S. Patent No. 6,172,050.

Claims 1-12 were rejected under 35 U.S.C. 103(a) as being unpatentable over Hilgard et al. Cancer Chemother. Phamacol, (1993) 32:90-95 and Stekar et al. European J. of Cancer, (1995) Vol. 31(3) pp 372-374 in view of Nössner et al. U.S. Patent No. 6,172,050. The Office Action contends that Hilgard and Stekar teach a combination of miltefosine with either cisplatinum or cyclophosphamide. The Office Action further alleges that Nössner discloses compounds of Formula II (as presently claimed) which are used in the treatment of breast cancer. Furthermore, The Office Action states that with respect to Nössner, "Column 19, lines 34-35 teach that that the above compound can be administered in a regimen and lines 48-54 teaches the

different agent that the above compound formula can be combined with cisplatin, cyclophosphamide (see col. Lines 50-51) in a pharmaceutically effective amount (see col. 20, lines 42-44) in a carrier or excipient (see same col.)." Finally, the Office Action argues that it would have been obvious to combine the cited references being that compounds of Formula I and Formula II have been used prior to the claimed invention in the treatment of breast cancer.

Applicants respectfully disagree with the Examiner's contention that Nössner teaches that compounds of Formula II can be combined with cisplatin or cyclophosphamide. The Office Action refers to Column 19, lines 48-54 in support of the position that Nössner teaches such a combination. However, lines 48-54 of Nössner read as follows:

> Treating the DMBA-induced mammary carcinomas in test rats and the KB imolanted tumors in test mice with standard cytostatics (e.g., Cyclophosphamide, Cisplatin and Adriamycin) proved relatively ineffective. The result demonstrates that the compounds described herein are superior to presently known cytostatics employed clinically in the treatment of tumors.

In this passage, Nössner is comparing the efficacy of heterocyclic alkylphosphocholines (such as those of Formula II of the present invention) with conventional cytostatics, including cisplatin and cyclophosphamide. The data revealed that the conventional cytostatics were "ineffective" while the heterocyclic alkylphosphocholines were quite effective. In fact, Nössner states that three of the heterocyclic alkylphosphocholines "are capable of effecting tumor remission, leading to a complete disappearance of tumors." Column 19, lined 44-46.

Therefore, it is clear that Nössner in fact teaches away from the claimed invention as currently amended. One of ordinary skill in the art certainly would not be motivated to combine a drug that was said to be "ineffective" in treating mammary carcinoma with a drug that was "capable of effecting tumor remission." Placing a known toxic agent with the heterocyclic alkylphosphocholine is contrary to reason, particularly if it were believed that the toxic agent was not effective in controlling the pathological disorder. The Examiner is reminded that "it is improper to combine references where the references teach away from their combination. *In re*

Grasselli, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir 1983). Therefore, Applicants argue that the Nössner reference has been improperly applied.

The Hilgard and Stekar references have been discussed in the preceding section. Stekar discloses pretreating rats with subcutaneous nenzo(a)pyrene-induced sarcomas with miltefosine prior to undergoing treatment with cyclophosphamide. Hilgard discusses one particularly study where miltefosine was combined with a cisplatin derivative or cyclophosphamide. Neither of the references discloses or suggests the use of heterocyclic alkylphosphocholines in the treatment of mammary carcinoma. On the other hand, Applicants show that the combination of a heterocyclic alkylphosphocholine with a traditional chemotherapeutic agent leads to "reduction in the tumor that was distinctly greater and longer through the combination treatment than through the single treatment in each case." See Examples 1-3 of the pending application.

One can only determine the advantageous of using the heterocyclic alkylphosphocholines applied in the present invention with hindsight. As stated above, it is impermissible to engage in a hindsight reconstruction of the claimed invention, using the Applicant's structure as a template, and selecting elements from references to fill in the gaps. *Interconnect Planning*, 744 F.2d 1132, 1143 (Fed. Cir. 1985). This point is further highlighted by the fact that the secondary Nössner reference applied by the Examiner suggests the undesirability of the presently claimed combination.

Consequently, withdrawal of the Section 103 rejection is earnestly requested.

CONCLUSION

Based on the foregoing amendments and remarks, favorable consideration and allowance of all of the claims now present in the application are respectfully requested.

Should the Examiner require or consider it advisable that the specification, claims and/or drawings be further amended or corrected in formal respects in order to place the case in condition for final allowance, then it is respectfully requested that such amendment or correction be carried out by Examiner's Amendment and the case passed to issue. Alternatively, should the Examiner feel that a personal discussion might be helpful in advancing this case to allowance, the Examiner is invited to telephone the undersigned.

The Commissioner is authorized to charge any required fees, including any extension and/or excess claim fees, any additional fees, or credit any overpayment, to Goodwin Procter LLP Deposit Account No. 06-0923.

Respectfully submitted for Applicant,

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